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Research Article

Is Obesity Associated with a Higher Risk of Differentiated Thyroid Cancer in a Cytologically Proven Series of Thyroid Nodules?

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Abstract: Background: Obesity and thyroid nodules have increased in frequency globally in recent years. Researchers are still exploring the complex relationship between obesity and cancer risk.

Objective: To determine the association between obesity with differentiated thyroid cancer (DTC) in patients presenting with thyroid nodules.

Materials and Methods: This cross-sectional study was performed in outpatient clinics of ENT department of Ruth K.M. Civil Pfau Hospital Karachi during 1st April, 2025 till 15th July, 2025. Thyroid ultrasound was performed by an experienced radiologist to confirm the presence of nodules, and patients meeting the criteria proceeded to cytological evaluation. The Bethesda classification was used to interpret Fine Needle Aspiration Cytology (FNAC) findings. Bethesda V and VI were interpreted as suspicious for malignancy and malignancy respectively.

Result: The number of studied patients were 314. Mean age was 43.6 ± 11.4 years. 69.7% of people were overweight or obese. 22.9% of cases fell under Bethesda categories 5 or 6. On univariate analysis, risk of Bethesda 5/6 finding was significantly lower in patients who were having normal weight and overweight as compared to obese patients. On multivariable analysis, risk Bethesda 5/6 finding was lower in overweight patients than obese patients but there no significance of lower risk in patients with normal body mass index (BMI) levels than obese patients.

Conclusion: While obesity was found to have a greater risk of differentiated thyroid cancer in univariate analysis, this was not consistently significant in all BMI categories in multivariable analysis. Therefore, the current study did not demonstrate a clear association of BMI and DTC cancer.

Keywords: Body mass index, Obesity, Thyroid nodules, Differentiated thyroid cancer, Fine needle aspiration cytology, Follicular neoplasm.

INTRODUCTION

Globally, the prevalence of obesity has more than tripled since 1975 and continues to rise [1]. People's health-related quality of life (HRQL) is significantly impacted by overweight and obesity, which is the major public health issues facing the globe today [2]. According to the World Health Organization (WHO), around 2.5 billion persons aged 18 and over, or 43% of the world's adult population, were overweight as of 2022, with 890 million (16%) being obese [3]. 37% of people worldwide are overweight or obese, regardless of their financial situation [1]. The prevalence in the WHO South-East Asia Region was 31% [4].

Obesity and overweight are now major risk factors for non-communicable diseases (NCDs), and their prevalence is rising at an unacceptably fast rate globally [5]. There is growing evidence that a variety of malignancies are linked to the risk of obesity in addition to their association with cardio metabolic disorders. These malignancies include cancers of the colon, endometrial, postmenopausal, renal, esophageal, pancreatic, liver, thyroid, and esophageal adenocarcinoma [1, 5]. It was demonstrated by International Agency for Research on Cancer (IARC) Working Group based on based on a review of over 1,000 studies that indicated an evidence connecting higher body fat percentages to an elevated risk of several types of cancer [6].

Over the last some decades, the occurrence of thyroid nodules has risen in parallel with the increasing global rates of obesity [7-9]. In the past thirty years, thyroid nodules incidence has dramatically amplified, owing largely to the incidental discovery of asympotomatic thyroid nodules in the context of a physical examination or imaging. Nodule evaluation is typically considered in regard to nodules over 1-1.5cm, with fine needle aspiration (FNA) being the primary method in an attempt to rule out malignancy; unsurprisingly, associated with the increased number of nodules evaluated, we have also seen a rise thyroid cancer occurrence [2,3]. While there is a partial explanation provided by improvements in diagnostic techniques to account for the increasing trend for differentiated thyroid cancer (DTC), there is also a rising incidence of more aggressive tumors on histology. This observation has led some researchers to speculate that as these tumors progress, regional risk factors may be introduced, such as radiation exposure, environmental toxins, or dietary factors [10-12].

While the linkage between obesity and cancer risk is probable to be complex and not fully understood, there are numerous possible mechanisms that could explain some of the association.

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These include insulin resistance and hyperinsulinemia, hormone imbalances, changes in hormone-signaling pathways, circadian rhythm problems, as well as changes in the gut microbiome, to name a few [13]. Hyperinsulinemia, insulin resistance and chronic pro-inflammatory state could also influence thyroid carcinogenesis via insulin receptors overexpression in thyroid carcinoma cells [14]. Layegh P. and colleagues found no big difference in how often thyroid nodules showed up in obese and non-obese people. But people with insulin resistance had more thyroid nodules. The research also showed that BMI had a strong connection to thyroid size [15]. The same observation was seen in a research conducted in morbidly obese individuals and found that women with morbid obesity had a significantly lower prevalence of thyroid nodules, especially solid ones [16]. Some more studies found no correlation with specific aggressive histopathological features of differentiated thyroid cancer (DTC) in patients who are obese [17, 18].

Obesity is on the rise in many lower middle income and middle income countries (LMICs), including Pakistan, due to a nutrition transition of greater ultra-processed food consumption and lower levels of physical activity [19]. Consequently, as obesity continues to rise so does its associated non-communicable diseases, creating a major public health issue. Emerging evidence suggest that obesity might be associated with differentiated thyroid cancer (DTC), but not in a direct manner; these mechanisms could be through insulin resistance, hormonal imbalance, and chronic inflammation. However, the literature continues to yield conflicting conclusions. Thus, the aim of this study is to determine the association between obesity with DTC in the local population of Karachi.

MATERIALS AND METHODS

This cross-sectional study was performed in outpatient clinics of ENT department of Ruth K.M. Civil Pfau Hospital Karachi during1st April, 2025 till 15th July, 2025. The study was commenced after acquiring formal permission from ethical review board with letter bearing reference numberIRB-3409/DUHS/Approval/2024/91.

The study included patients of either gender of age 18 years or above with a diagnosis of thyroid nodule on ultrasound. Pregnant females and lactating women, patients with history of prior neck surgery or radiation, serious cardiopulmonary, hepatorenal, and coagulation disorder, and a family history of thyroid cancer were excluded.

Sample size was determined using 27.5% frequency of Bethesda V/VI in thyroid nodules patients [20], 95% confidence interval and a 5% margin error, yielding a sample size of 307 patients. Online available calculator Open-Epi was utilized to performed sample size calculation. Using non-probability consecutive sampling method patients were enlisted.

All eligible patients went through a detailed clinical assessment at the time of their first outpatient visit. Demographic data including age and gender and relevant clinical history were collected in structured questionnaire. Thyroid ultrasound was conducted by a radiologist expert, and all in accordance with the criteria, in case of the positive results nodules was conducted cytological examination. Using a 23/25-gauge needle, FNAC was carried out under ultrasound guidance. The sample was allowed to air dry, stained with May-GrünwaldGiemsa stain, and then examined by qualified cytologists for interpretation. The Bethesda classification comprised six categories based on the criteria used to report cytological results: benign (Bethesda II), atypia of unknown significance or follicular lesion of unknown significance (AUS/FLUS, Bethesda III), follicular neoplasm or suspicious for follicular neoplasm (FN/SFN, Bethesda IV), suspicious for malignancy (SM, Bethesda V), and malignant (Bethesda VI).

Patients' height and weight were measured using standardized techniques. Body mass index was calculated by dividing weight with square height in Kg/m^2. The BMI was classified into five categories using thresholds for Asian adults: 18.5 (underweight), 18.5-22.9 (normal weight), 23.0-24.9 (over-weight), ≥25 (obese).

STATISTICAL ANALYSIS

Data analysis was done using IBM SPSS for Windows, Version 27 (Armonk, NY: IBM Corp). Frequencies and percentages were computed for categorical variables. Numerical variables were presented as mean ± standard deviation. Binary logistic regression was applied to ascertain association of patients' features with DTC. Variables with $p<0.25$ in univariate analysis were entered in final multivariable regression model. P-values ≤0.05 was deemed as statistically significant on final regression model.

RESULT

In this study, 314 patients were evaluated. Mean age and BMI of patients was 43.6 ± 11.4 years and 24 ± 2.5 Kg/m^2. Out of 314 patients, 43.3% were 50 years of age or older, while the majority (56.7%) were under 50 years. According to body mass index, 69.7% of people were overweight or obese, whereas 30.3% were of normal weight. 23.2% of patients had high blood pressure, while 33.4% had diabetes. According to findings from FNAC, 22.9% of cases fell under Bethesda categories 5 or 6. Nodules were 20 mm or larger, with the largest group (38.9%) measuring 40mm or more. Compared to single nodules, more patients had multiple nodules (61.5%) (Table **1**).

On univariate analysis risk of Bethesda 5/6 finding was significantly lower in patients with age group < 50 years as compared to those who were ≥50 years older. Risk of Bethesda 5/6 finding was significantly lower in patients who were having normal weight and overweight as compared to obese patients. Odds of Bethesda 5/6 were significantly higher in diabetic patients. The risk of Bethesda 5/6 was significantly lower in those having thyroid nodule of size 10-20mm and multiple nodules (Table **2**).

Table 1. Summary of Descriptive and Clinical Features of Patients.

Variables	Groups	Frequency (%)
Age	<50 years	178(56.7)
	≥50 years	136(43.3)
Body Mass Index	Normal Weight (18.5-22.9)	95(30.3)
	Over Weight (23.0-24.9)	131(41.7)
	Obese (25-30)	88(28)
Hypertension	Yes	73(23.2)
	No	241(76.8)
Diabetes Mellitus	Yes	105(33.4)
	No	209(66.6)
FNAC Findings	Bethesda 1	31(9.9)
	Bethesda 2	111(35.4)
	Bethesda 3	62(19.7)
	Bethesda 4	38(12.1)
	Bethesda 5/6	72(22.9)
Mean Size Nodule	<10mm	7(2.2)
	10-20mm	32(10.2)
	20-30mm	83(26.4)
	40mm and Above	122(38.9)
	30-40mm	70(22.3)
Number of Nodules	Multiple	193(61.5)
	Single	121(38.5)

Table 2. Association of Patients' Features with Differentiated Thyroid Cancer on Univariate Analysis.

Variables	Groups	DTC		OR (95% CI)	p-value
		Yes n(%)	No n(%)		
Age	<50 years	16(9)	162(91)	0.14 (0.1-0.3)	**<0.001
	≥50 years	56(41.2)	80(58.8)	Reference category	
Gender	Male	34(47.2)	123(50.8)	0.87 (0.51-1.46)	0.591
	Female	38(52.8)	119(49.2)	Reference category	
Body Mass Index	Normal Weight (18.5-22.9)	6(6.3)	89(93.7)	0.08 (0.04-0.22)	**<0.001
	Over Weight (23.0-24.9)	28(21.4)	103(78.6)	0.35 (0.19-0.64)	**<0.001
	Obese (25-30)	38(43.2)	50(56.8)	Reference category	
Hypertension	Yes	17(23.3)	56(76.7)	1.02 (0.55-1.90)	0.934
	No	55(22.8)	186(77.2)	Reference category	
Diabetes Mellitus	Yes	37(35.2)	68(64.8)	2.70 (1.57-4.64)	**<0.001
	No	35(16.7)	174(83.3)	Reference category	
Mean Nodule Size	10-20mm	4(12.5)	28(87.5)	0.25 (0.08-0.78)	*0.018
	20-30mm	15(18.1)	68(81.9)	0.48 (0.22-1.02)	0.057
	40mm and Above	31(25.4)	91(74.6)	0.74 (0.39-1.42)	0.370
	30-40mm	22(31.4)	48(68.6)	Reference category	
Number of Nodules	Multiple	17(8.8)	176(91.2)	0.12 (0.06-0.21)	**<0.001
	Single	55(45.5)	66(54.5)	Reference category	

CI: Confidence interval, OR: Odds ratio, *Significant at p<0.05, **Significant at p<0.01.

On multi-variable analysis, younger age and presence of multiple nodules were still associated with lower risk of Bethesda 5/6 finding. Risk Bethesda 5/6 finding was lower in overweight patients than obese patients but there no significance of lower risk in patients with normal BMI levels than obese patients (Table **3**).

Table 3. Association of Patients' Features with Differentiated Thyroid Cancer on Multivariable Analysis.

Variables	Groups	Adjusted OR	95% CI	p-value
Age	<50 years	0.28	0.12-0.65	*0.003
	≥50 years	Reference category		
Body Mass Index	Normal Weight (18.5-22.9)	0.37	0.12-1.25	0.112
	Over Weight (23.0-24.9)	0.38	0.18-0.81	*0.012
	Obese (25-30)	Reference category		
Diabetes Mellitus	Yes	1.75	0.87-3.56	0.138
	No	Reference category		
Mean Nodule Size	10-20mm	0.75	0.20-2.90	0.679
	20-30mm	1.26	0.50-3.22	0.623
	40mm and Above	1.85	0.74-4.60	0.188
	30-40mm	Reference category		
Number of Nodules	Multiple	0.13	0.07-0.27	**<0.001
	Single	Reference category		

CI: Confidence interval, OR: Odds ratio, *Significant at p<0.05, **Significant at p<0.01.

DISCUSSION

This study examined the relationship between obesity and the risk of developing differentiated thyroid cancer (DTC) in patients with thyroid nodules. Our findings provide insight into important relationships of DTC with age, body mass index (BMI), diabetes, and the number of thyroid nodules. These findings provide us with important indications on the factors that may indicate thyroid nodule malignancy.

It's important to note that 56.7% of the study participants were under 50 years old. Most patients (69.7%) were overweight or obese, and many also had additional health conditions such as high blood pressure (23.2%) and diabetes (33.4%). These findings are consistent with what we observe occurring globally. The average age of those with thyroid cancer is under 50 years old, according to multiple studies [21-23].While Li CL *et al.* found that around half of a sample of patients with pappillary tumors were either overweight or obese (50.4%) [21], Matrone A *et al.* found that over half of the DTC patients had a BMI categorized as overweight or obese (56.5%) [24]. Similarly, the Saudi Arabian study discovered that nearly a quarter of patients with thyroid nodules had diabetes (24%) and hypertension was prevalent in 22.5% [25]. Our findings were supported by a large cross-sectional study conducted in Southwest China, which found that people with thyroid nodules had a much higher prevalence of diabetes mellitus (50.1%) and hypertension (45.6%) than those in our group [26]. These results emphasize the increasing burden of metabolic disease in individuals with thyroid nodular disease.

According to Bethesda categories 5 or 6, our study sample had a DTC prevalence of 22.9%. This is comparable to a local study conducted in Pakistan that showed a 27.5% Bethesda V/VI in 120 patients with thyroid nodules [20]. Another study indicated that in patients with thyroid solitary nodules, 22.4% of suspicious FNAC results had 20% confirmed malignancies [27]. However, there is a great deal of diversity when compared to worldwide literature. According to a Saudi Arabian study Bethesda V (suspicious for malignancy) and VI (malignant) were detected in 3.5% and 6.1% of the 310 thyroid nodule evaluation records based on FNAC, respectively [28].Only 15% of thyroid nodules in a large US study of 1259 patients were found to be malignant [29]. There could be a variety of reasons for this variation between researches. Variability in prevalence may be explained by differences in cytopathologist experience, FNAC procedure, underlying population risk, patient selection, and institutional recommendations for FNAC.

Our results indicate a significant negative correlation between DTC and younger age (less than 50 years). Both univariate and multi-variable analysis showed that the (younger) age variable was significantly associated with a decreased risk of Bethesda 5/6 categorization. This is in line with earlier research showing the higher incidence and usual aggression of thyroid cancer in older adults [30, 31]. Numerous staging systems for thyroid carcinoma have included age as a prognostic factor [32].Our findings add to the literature that age serves as an important risk stratifier when assessing thyroid nodules for malignancy.

A main purpose of our study was to evaluate the relationship between obesity and differentiated thyroid cancer (DTC). We found that in univariate analysis, both normal-weight and overweight individuals were significantly less likely to be classified as Bethesda 5/6 compared to obese individuals. While overweight

individuals had a significantly reduced risk when compared to obese patients, this trend was not seen in normal-weight individuals after adjustment indicating no consistent dose–response relationship. Nevertheless, underlying biological mechanisms including insulin resistance, chronic inflammation, high leptin concentrations and raised TSH support a role for obesity in thyroid carcinogenesis [33].There is now empirical evidence that supports this connection. In 2023, a meta-analysis of 22 cohort studies found a 33% increased risk for thyroid cancer among obese individuals (RR = 1.33, 95% CI 1.24–1.4) [34]. In a more recent meta-analysis (2024) investigation with 27 cohort studies, the pooled effect estimate for the association of indicators for adiposity (including BMI) and thyroid cancer risk was 1.16 (95% CI 1.12–1.21) [35]. The overall lack of protective association for individuals with normal BMI, as observed in our study, suggests that unmeasured factors that could potentially include fat distribution, metabolic syndrome, or genetic susceptibility, may interact with our measures to influence risk. Thus, there is need for further investigation incorporating precision measures of metabolism to help us better understand this complex association pattern.

Diabetes mellitus was strongly associated with DTC on univariate analysis (OR 2.70, $p<0.001$), which suggests that there are more odds of malignancy in individuals with diabetes. This may have an association with hyperinsulinemia, and the insulin-like growth factors, which may help to promote tumor growth [33]. Previous studies have also reported similar associations with diabetes and thyroid cancer. However, the association lost significance in our multi-variable model indicating potential confounding due to age or BMI. More prospective research is needed to define the potential independent relationship that diabetes may have.

Interestingly, patients with multiple nodules were significantly less likely to have DTC than patients with solitary nodules. Both univariate and multi-variable analyses indicated that multiple nodules were associated with a significantly reduced risk of Bethesda 5/6 category. This is significant, especially for clinical management and treatment decisions. Solitary nodules are traditionally recognized as more suspicious for malignancy than multiple nodules, which typically characterized as benign features of multi-nodular goiter. With this finding, we reinforce the need for a nodule-specific rather than patient-level risk assessment approach. This work also supports the current guidelines to consider individual evaluation of each of nodule, such as ultrasound risk stratification models like ACR TI-RADS or the recommendations outlined in ATA guidelines.

Concerning nodule size, most nodules in our cohort were over 20 mm in size, and the greatest proportion was in the ≥40 mm category. However, no consistent relationship existed with nodule size and DTC risk in adjusted analyses. While small nodules (10-20 mm) had lower odds in univariate analysis this association did not hold in the multi-variable model most likely due to lower sub-group size (n=10.2%). The potential for nodule size to predict malignancy has remained controversial, including sources which found no relationship [36, 37]. While it was also reported in a study that when a type of thyroid malignancy was examined, the rates of follicular carcinoma and other rare malignancy were reported to increase with increasing nodule size [38].

Our investigation provides important insights by focusing on cytologically confirmed thyroid nodules and also predictors of high-risk categories (Bethesda 5/6). The study is strengthened by the use of both univariate and multi-variable logistic regression analyses to account for confounding variables. The study provides important regional data on thyroid cancer that may help provide better insight into the disease in South Asian populations, as this is a group where both obesity and thyroid disorders are on the rise.

LIMITATIONS

While our study has a number of strengths, it is also important to acknowledge a few limitations. First, due to the cross-sectional study design, it is difficult to infer causation of obesity on thyroid cancer risk. Second, FNAC results were used as a surrogate marker of malignancy, although the Bethesda 5 and 6 is suggestive of cancer, histopathological confirmation would have provided a clearer conclusion. Third, the categorization of BMI categories was based upon standard cut-offs and may not delineate the body composition differences or metabolic health status. Fourth, since a number of potentially important variables were not captured in the analysis (e.g., TSH levels, family history of thyroid cancer, ultrasound characteristics), it is possible that the results of the analysis would be affected in some way. Finally, the study was done in a single tertiary care center and conclusions may not be easily generalized to the broader population.

CONCLUSION

While obesity was found to have a greater risk of differentiated thyroid cancer in univariate analysis, this was not consistently significant in all BMI categories in multi-variable analysis. Therefore, the current study did not demonstrate a clear association of BMI and DTC cancer.

ABBREVIATIONS

AUS: Atypia of unknown significance.

BMI: Body mass index.

DTC: Differentiated thyroid cancer.

FLUS: Follicular lesion of unknown significance.

FN: Follicular neoplasm.

FNAC: Fine Needle Aspiration Cytology.

HRQL: Health-related quality of life.

IARC: International Agency for Research on Cancer.

LMICs: Lower middle income and middle income countries.

NCDs: Non-communicable diseases.

SFN: Suspicious for follicular neoplasm.

SM: Suspicious for malignancy.

WHO: World Health Organization

AUTHORS' CONTRIBUTION

Irfan Ahmed Shaikh: Conceptualization, Study Design, Writing Draft, Final approval, final proof to be published.

Danish Ur Rehman: Study Design, Critical review and revision the manuscript.

Sidra Bano and Rajesh Kumar: Writing Draft.

Ramsha Khalid and Raheem Bakhsh: Methodology, Data analysis and interpretation.

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Declared none.

ETHICAL DECLARATIONS

Data Availability Statement

Data will be available from the corresponding author upon a reasonable request.

Ethical Approval

The study was commenced with the approval of Institutional Review Board of Dow University of Health Sciences (IRB-3409/DUHS/Approval/2024/91).

Consent to Participate

All the study participants were enlisted with their written informed consent.

Consent for Publication

All authors give consent for the publication of this work

Conflict of Interest

Declared none.

Competing Interest/Funding

Declared none.

Use of AI-Assisted Technologies

The authors declare that no generative artificial intelligence (AI) or AI-assisted technologies were utilized in the writing of this manuscript, in the creation of images/graphics/tables/captions, or in any other aspect of its preparation.

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